Overexpression of stomatin-like protein 2 drives epithelial mesenchymal transition in pancreatic cancer and leads to poor prognosis.

（書式１８）課程博士

学　位　論　文　要　約

博士論文題目　Overexpression of stomatin-like protein 2 drives epithelial mesenchymal transition in pancreatic cancer and leads to poor prognosis.(Stomatin like protein 2 の過剰発現は、膵臓癌における EMT を誘導することで再発率および死亡率を増悪させる)

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【Background】Pancreatic cancer (PC) is one of the most dismal types of cancer. Researchers at my institute identified stomatin-like protein 2 (SLP-2) as a new PC prognostic marker by mass-spectrometry based proteomics analysis using formalin-fixed paraffin-embedded tissues. SLP-2 is located mainly in mitochondria and regulates their stability. SLP-2 expression correlates with the malignant prognosis of different cancers. However, detailed analyses and the pathogenetic mechanisms explaining their correlation remain unclear for PC.

【Aim】To elucidate the SLP-2 pathogenic mechanisms and their correlation with prognosis in patients with PC.

【Method】Microarrays were used to detect altered gene expression profiles in tumor cells, as well as in vitro analyses such as migration and invasion assays. A splenic injection model was used to confirm the SLP-2 function in SCID mice. Finally, the clinicopathological characteristics (including SLP-2 immunohistochemical staining) and prognoses of 202 patients with PC were retrospectively reviewed.

【Result】Microarray analyses revealed several epithelial mesenchymal transition(EMT)-related genes with altered expression in PC cells with both high and low SLP-2 expression. In SLP-2 silenced cells, the expression of e-cadherin was elevated, and those of vimentin and ZEB1 were decreased. Migration and invasion activities were also decreased in cells with reduced SLP-2 expression. SLP-2 was expressed mainly in the mitochondrial fraction and its silencing decreased the glucose uptake of cancerous cells. In vivo analyses demonstrated that the number of liver metastases was significantly reduced in cells with low SLP-2 expression. Patients with high SLP-2 expression showed worse disease-specific survival (DSS) ($P < 0.001$) and recurrence-free survival (RFS) ($P < 0.001$) than those with low SLP-2 expression. Moreover, my analyses indicated that SLP-2 expression may serve as a predictive factor of DSS (hazard ratio [HR] 2.18; $P < 0.001$) and RFS ([HR] 1.63; $P = 0.027$).

【Conclusion】SLP-2 expression may be useful as a predictive factor of recurrence and survival after curative resection in PC. SLP-2 exerts its malignant function by driving the metastatic potential via its EMT pathway regulation.